QbD Assisted Design and Development of Mesoporous Drug Delivery System for Cancer Therapy

Abstract of proposed work plan/ problem

Cancer is the leading cause of death worldwide. Poor solubility of anti-cancer drugs is major problem in dosage form development. Nanoparticle based drug delivery systems have provided unique approaches for cancer treatment. Early clinical results suggest that nanoparticle based treatments can show enhanced efficacy, while simultaneously reducing side effects by localizing in tumors. Increasing cell survival in cancer chemotherapy is an important challenge for the field of medicine. Drug release from mesoporous silica nanoparticles (MSNs) pores constitutes one of the superior features of MSNs. The nanoparticles can be functionalized with small molecule-based ligands for active targeting. Furthermore, these MSNs can overcome major problem associated with most of drugs i.e. poor aqueous solubility. An anticancer drug can be loaded in the pores of folate-functionalized MSNs for intracellular drug delivery. The release rates of drug from the nanoparticles may increase under acidic conditions, and might be favourable for controlled drug release to cancer cells. The literatures suggest that MSNs may serve as promising drug carriers for application in cancer therapy and cell targeting are simultaneously possible using a multifunctional mesoporous silica nanoparticle**.**

Keywords: Cancer, solubility, meso porous silica, nano particles, folate etc.

1. Introduction

Cancer is the leading cause of death worldwide. Around 8.2 million people die each year from cancer, an estimated 13% of all deaths worldwide. Approximately 70% the increase in new cases of cancer expected over the next 2 decades [1]. Major problem associated with conventional chemotherapy is its clinical inefficiency and serious side effects, mainly because of the leaking out of drugs during blood circulation and nonspecific cell/tissue bio-distribution. Use of nanotechnology based drug delivery systems can solve these problems [2, 3]. Nano carriers have advantages of surface properties and nano scales exhibiting improved local drug concentration and reduce nonspecific tissue bio-distribution[4-6].The most commonly used nano-vehicles include liposomes[7], micelles[8], dendrimers[9], nanoparticles[10], and inorganic materials[11]. Among inorganic materials, mesoporous silica nanoparticles (MSNs) have rapidly developed into an important candidate for nano medical applications since a MCM-41 type mesoporous silica material was first reported as a drug delivery system in 2001[12]. The MSNs enjoy advantages like simple, scalable, and cost effective fabrication, as well as nontoxic nature, large surface area and pore volume, and high density silanol containing surface. Moreover, the nano tunnels that encapsulate cargoes can be sealed with various gatekeepers, and such cargoes will not be released until triggered by stimuli, which offers an opportunity to design stimuli responsive drug delivery systems for controlled release. Mesoporous silica nanoparticles have been reported as promising drug vehicles due to the mesopore structure, chemical stability, surface functionality, and biocompatibility [13].

2. Review of Literature and Development in the subject (Previous work done in the relevant area)

1. Kendre et. al, (2015); developed oral nanocurcumin delivery to improve quality of life of cancer patients. [14].
2. Kempen et. al, (2015); investigated a biodegradable MSN with ultrasound and MR imaging capabilities and have used it as a theranostic tool with mesenchymal stem cells [15].
3. Nakamura et. al, (2015); successfully developed a novel drug carrier based on a multimodal imaging agent, mFLAME, which consists of a PFCE core and mesoporous silica shell. The silica shell of mFLAME imparted various practical and useful properties such as dispersibility in water, chemical surface modiability, biocompatibility, and efficient drug loading and release capacities [16].

4. Goscianska et. al, (2015); modified SBA-15 and Cubic mesoporous silica KIT-6 with lanthanum, They obtained materials of hexagonal and regular structure by the hydrothermal method using a triblock copolymer Pluronic P123 as a template. The mesoporous silicas were impregnated with an aqueous solution of lanthanum (III) chloride in the amount necessary to obtain 1, 3 and 5 wt. % La loading. The high coverage of lanthanum on the surface of KIT-6 and SBA-15 solids was found to increase the amount of ibuprofen and the rate of its release. [17].
5. Lu et.al, (2012); studied *in vivo* tumor suppression efficacy of mesoporous silica nanoparticles-based drug-delivery system. In this study, mesoporous silica nanoparticles were used as chemotherapy delivering agents in two different human pancreatic cancer xenografts and different mouse species. Significant tumor-suppression effects, biocompatibility and efficient renal clearance are demonstrated [18].

3. Objectives of Research/ Proposed Hypothesis

- To develop anticancer drug loaded mesoporous silica for applications in cancer
- To overcome the insolubility problem of anticancer drug
- To utilize mesoporous silica nano particles (MSNs) as a drug-delivery vehicle for delivering anticancer drug to tumors and suppressing tumor growth
- To explore MSNs as a stable, biocompatible, and effective therapeutic agent for cancer therapy.

3. Methodology to be adopted

The mesoporous silica template will be synthesized by using suitable method and will be subjected to various sophisticated analytical techniques like SEM, TEM, DSC, XRD, Mercury Porosimetry or BET Analyzer for detailed characterization. After confirmation of organized structure of mesoporous silica, the anticancer drug will be loaded. Work will be performed to improve flow property of mesoporous silica and suitable dosage form will be developed (by using QbD approach). The developed dosage form will be characterized by necessary parameters. It will be directed towards malignant cells in-vitro and in-vivo by using specific cancer cell line study.

4. Importance of study/ Society application:

National and International status

i. Curcumin coated magnetite nanoparticles for biomedical applications (WO2013108270 A1). The present invention discloses biocompatible, stable curcumin or its derivatives coated ultra -small super paramagnetic iron oxide nanoparticles (USPION) for biomedical applications.

ii. Mesoporous silicon (WO 2012114126 A1). This invention relates to mesoporous silicon, methods for making mesoporous silicon, mesoporous silicon obtainable from said methods and uses of the mesoporous silicon. In particular, the mesoporous silicon may be mesoporous amorphous silicon or comprise at least some mesoporous amorphous silicon. In addition, this invention relates to mesoporous silicon which may be derived from plants, particularly land based plants.

iii. Charged mesoporous silica nanoparticle-based drug delivery system for controlled release and enhanced bioavailability (US 8252337 B2). A charged mesoporous silica nanoparticle (MSN)-based drug delivery system for controlled release and enhanced bioavailability is disclosed. The system comprises a positively charged MSN, which has a silica matrix and an array of pores and/or nanochannels in the matrix. The entire substance of the matrix, all the surfaces and the pores and/or nanochannels comprise a plurality of silanol (Si—OH) and quaternary ammonium functional groups.

Significance of the study

Low drug solubility in aqueous media of most anticancer drugs is major hurdle in the development of new delivery systems. Drug loading within mesoporous silica nanoparticles (MSNs) provides advantages when using water insoluble anticancer drugs by incorporating them into the matrix of MSNs. The drug loaded MSN can directly delivered to malignant cells and ultimately it will reduce the toxic effects of drug to normal flora of cells.

5. Proposed work Plan/ Formulation and Structure of Study

Literature survey

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Selection and procurement of materials

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Synthesis of mesoporous template (Mesoporous Silica Nano Particles: MSNs)

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Drug loading

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Characterization

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Improvement in flow property of mesoporous material

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Development of dosage form by QbD approach

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Characterization of dosage form

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IVIVC study

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Comparison with marketed preparation

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Data compilation

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Paper publication

Year-wise Plan of work and targets to be achieved

Year	**Work to be completed**		
1st	➢ Literature survey ➢ Selection and procurement of materials	➢ Synthesis and characterization of mesoporous template ➢ Drug loading	Characterization of drug loaded template
2nd	Improvement in flow property of mesoporous	Dosage form development by QbD approach	Characterization of dosage form
3rd	IVIVC study	Comparison with marketed preparation	Data compilation

6. References

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